PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.02.2004
Applicant's or agent's file reference: P029491WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00301	23.01.2003	24.01.2002

Applicant
HEIGHTMAN, Nicholas John et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P029491WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00301	23.01.2003	24.01.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K9/00		
Applicant		
HEIGHTMAN, Nicholas John et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.08.2003	20.02.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00301

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2 received on 14.01.2004 with letter of 13.01.2004

Claims, Numbers

1-9 received on 14.01.2004 with letter of 13.01.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	1-5,7-9
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	-

2. Citations and explanations

see separate sheet

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: EP 0 306 469
D2: GB 993 308
D3: US 5 939 127

2 **NOVELTY** (Art. 33(2) PCT)

2.1 D1 discloses cookies having a filling comprising psyllium with increased palatability for control of blood cholesterol levels in the relevant amounts. Other agents may be added (D1, page 4, lines 36-42; page 4, lines 47-50; examples 1-3). Also the biscuit layers comprise a medical substance, in that in Example 2 sodium bicarbonate is used.

2.1.1 Also other ingredients of the dough can be interpreted in broad terms as medical substance, due the absence of a clear meaning of the term "medicinal substance as used in compliance with a drug treatment dosage regime". This formulation is suitable for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime. The result to be achieved of claim 7 can not confer novelty as the claim does not have a technical feature disclosing how this effect can be achieved.

2.2 D2 discloses sandwich biscuits having a filling comprising a bulking agent such as carboxymethyl cellulose (D2, page 1, right column, lines 47-60 and lines 82-86; examples 1 and 2).

2.2.1 This formulation is suitable for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime.

2.3 D3 discloses cookies filled with a cream, said cream comprising inulin (D3, column 2, lines 37-47; column 5, lines 45-53; example 1).

2.3.1 This formulation is suitable for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime. Inulin is used in

diabetic patients and as diagnostic agent.

2.4 In view of D1-D3, the present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 1-5,7-9 is not new.

2.5 In view of the prior cited, claim 6 appears to be novel and meets therefore the requirements of Art. 33(2) PCT.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 Claims 1-5,7-9 do not involve an inventive step, because they are not new.

3.2 Even if the applicant could restore novelty of independent claim 1, an objection on ground of lack of an inventive step is likely to arise. Indeed, having regard to the claimed composition and the prior art, the person skilled in the art would regard the composition of the present invention (as far as novel) as an obvious alternative to those known.

3.3 Dependent claim 6 does not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step for the following reasons:

3.3.1 It seems to be a straightforward possibility to employ the invention of D1 for taste masking of known bad-tasting drugs. The person skilled in art could hereby reasonably expect success in applying the solution of taste masking of the prior art to the known problem, that is an otherwise unpalatable medicament.

3.4 Novelty provided, in view of the above, the present application seems not meet the requirements of Article 33(3) PCT, because the claimed subject-matter does not involve an inventive step.

4 **Certain defects**

4.1 The relative term "cream filling" used in claims 1 and 7 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

FORMULATION FOR THE ADMINISTRATION OF MEDICINAL SUBSTANCES

FIELD OF INVENTION

This invention relates to a new formulation for the administration of medicinal substances within traditional baked food products, in particular within sandwich biscuits.

BACKGROUND OF THE INVENTION

Many medicines are potent materials requiring small amounts for their effectiveness, but there are other medicines that must be administered in large doses. Conventional formulations such as tablets and capsules can accommodate up to 1000mg of active ingredient but the products are very large and many patients find them difficult to swallow. In many cases the physical properties of the medicinal substance preclude dosages in excess of 250-500mg as they require dilution in inert materials to render them suitable for processing. Dosages of the order of several or many grammes per day require the patient to take many tablets. Some medicines such as cholestyramine resin are presented in sachets for dispersion in water. The products are not very palatable and are inelegant, again resulting in problems with patient acceptability and compliance.

It is known that medicines can be made more palatable or their presence disguised by incorporating the medicines within pre-cooked biscuits that have been reduced to crumb form. However, this requires intervention on behalf of the person making up the mixture and relies on their skill in ensuring that both a full dose of medicine is incorporated within the mixture and that the patient consumes all of the mixture. It is also known that certain therapeutic substances can be incorporated within biscuits during the initial cooking step, but this is not always satisfactory, particularly if the incorporated substance is adversely affected by the cooking process. There thus remains a need to provide alternative formulations for unpalatable medicinal, i.e. pharmaceutically active, substances.

It is the purpose of the present invention to allow the inclusion of active medicinal substances in readily acceptable formulations in such a way that compliance with drug treatment dosage regimes in enhanced. The present invention also addresses the problem of allowing large dosages of drugs to be administered effectively, especially as it has often not previously been convenient to administer such dosages by known administration routes. Many treatment regimes achieve sub-optimal therapeutic results because patients for whom the treatment is prescribed find that it is unpleasant to take the drug in the

inadequate quantities. The present invention permits the administration of large amounts of unpalatable material - for example with a gritty texture or a chalky texture or other unpleasant mouth feel, in a product which both palatable and familiar to the patient. This helps to ensure acceptability to the patient, and thereby improve patient compliance.

We have found that the formulation according to the present invention can be adapted to carry relatively high quantities of medicinal drug substances and combination of medicinal substances in such a way that chewing in the mouth facilitates swallowing. without adversely affecting the taste or mouthfeel of the biscuit. This makes the administration of drugs much more acceptable to many patients who find it difficult to swallow conventional pills and capsules. A further advantage is that formulations of the present invention have a texture that masks unpleasant mouth feel, such as gritty texture or chalkiness of some medicinal substances. The new formulations are also particularly suitable for the long-term administration of medicinal substances.

SUMMARY OF THE INVENTION

According to the present invention there further provided a formulation for the administration of a medical substance as used in compliance with a drug treatment dosage regime comprising a sandwich biscuit having two or more biscuit layers that support cream filling layer(s), in which the cream filling layer, and optionally the biscuit layers, comprise(s) a dosage unit form, or a multiple or sub-multiple thereof, of an unpalatable medicament. A further aspect of the invention is that the cream filling layer can contain a large amount of medicinal substance without having a deleterious effect on the mouth feel or palatability of the product.

The "sandwich biscuit" of the present invention may comprise a cream filling layer supported between any convenient number of dry layers, normally two layers, of biscuit. The biscuit layer of the sandwich biscuit may be a plain, non-medicated, biscuit layer or may itself contain a medicament. In the latter instance, it is possible to select a different medicament for the cream filler layer from that in the biscuit layer, whereby the two medicaments have a co-operating or synergistic effect. As already indicated, a medicine is unpalatable if it cannot be readily orally administered in its simple state, for example because of unpleasant mouth feel.

As indicated previously, the invention is of special value where relatively large amounts of active medicinal ingredient need be taken for the treatment to be effective, for

CLAIMS

1. A formulation for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime comprising a sandwich biscuit comprising two or more biscuit layers that support layers wherein the cream filling layer comprises a dosage unit form or multiple or sub-multiple thereof of an unpalatable medicament.

2. A formulation according to claim 1, in which the medicament has a gritty texture or a chalky texture or other unpleasant mouth feel.

3. A formulation according to claim 1 or 2, in which the medicament is present in an amount of greater than 500 mg per biscuit.

4. A formulation according to claim 3, in which the medicament is present in an amount of between 1g and 3g per biscuit

5. A formulation according to any of the foregoing claims, in which the medicinal substance is selected from the ion exchange resin substance VML252, optionally in combination of calcium carbonate, the ion exchange resin cholestyramine, optionally in combination chlofibrate, gemfibrozil and other orally active cholesterol-lowering materials, anthelmintic agents, metformin or gamma guanidinobutyramide and its pharmaceutically acceptable salts, optionally in combination of other oral agents used to treat diabetes type 2, optionally in combination with other agents for the oral treatment of obesity, and ion exchange resin suitable for treating elevated serum potassium, optionally in combination of with other oral agents used for treating elevated serum potassium.

6. A formulation according to claim 5, in which the anthelmintic agent is albendazole, febendazole, Ivermectin, thiabendazole and another bendazole substances

7. A formulation according to any of the foregoing claims comprising a biscuit layers comprise a medical substance, in which the medicinal substance in the biscuit and the

medicament in the cream filling layer have a co-operating or synergistic effect on administration.

8. A formulation according to any of claims 1 to 6, in which the biscuit layer is an oatmeal biscuit and the medicament is a cholesterol lowering pharmaceutical.

9. A formulation according to claim 1, substantially as hereinbefore described in any one of the Examples.